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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
PAPPU, SITA S	

ART UNIT	PAPER NUMBER
1632	7

DATE MAILED: 01/17/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/769,204	Applicant(s) ALISON ET AL.	
	Examiner Sita S Pappu	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 26-51 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 26-51 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Information disclosure statement filed on January 24, 2001 in Paper #4 has been entered. Preliminary amendment a (Paper #5, filed 01/24/01) and Preliminary amendment b (Paper #6, filed 01/24/01) have been entered. Claims 1-25 have been cancelled. Claims 26-51 have been newly added.

Claims 26-51 are pending in the instant application. This paper contains an examination of the claims 26-51, on their merits.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

> The oath or declaration is defective because:
> It does not state that the persons making the oath or declaration have reviewed and understood the contents of the specification, including the claims, as amended by any amendment specifically referred to in the oath or declaration.
>
> In particular, this application contents include two preliminary amendments (paper number 5 and paper number 6), and the oath or declaration does not indicate that all the applicants reviewed and understood the amendments made by paper numbers 5 and 6. The oath or declaration does not refer to these amendments to the application.

The wording of an oath or declaration cannot be amended. If the wording is not correct or if all of the required affirmations have not been made or if it has not been properly subscribed to, a new oath or declaration is required. The new oath or declaration must properly identify the application of which it is to form a part, preferably

by application number and filing date in the body of the oath or declaration. See MPEP §§ 602.01 and 602.02.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 28-51 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 28-51 are drawn to a method of treatment and to a method for treating or preventing cirrhosis of the liver by using a method for improving the efficiency of in vivo liver cell transduction, the said method of treatment comprising administering a composition comprising tri-iodothyronine (T3) and keratinocyte growth factor (KGF), and further comprising administering to the liver a retroviral vector complexed with the cationic liposome, DiOctadecylamidoGlycylSpermine or DOGS, subsequent to the induction of liver cell proliferation, thereby increasing transduction efficiency. The claims are broad enough to encompass the treatment of any disease or condition of the human or animal body, including diseases outside of the liver. However, one of skill in the art would not expect that a method that involves inducing liver cell proliferation and obtaining expression of a gene product in the liver would be useful, for example, in treating diseases of the brain.

While the specification discloses a method for improving the liver cell transduction efficiency, by administering a composition comprising tri-iodothyronine (T3) and keratinocyte growth factor (KGF), it does not disclose a method of treatment for any and all diseases. In particular, it does not disclose the method for treating or preventing cirrhosis of the liver. The specification does not disclose any protocols or steps, and, thus, does not satisfy the 'how to use' requirement of 35 U.S.C. 112, to practice the invention of claims 28-51, whereby the claimed therapeutic effect would result. While the skill of an artisan in this subject area is considered very high, without specific guidance and/or working examples it would require undue experimentation on the part of a skilled artisan to practice the invention of claims 28-51. It is noted that the law requires that the disclosure of an application shall inform those skilled in the art how to use applicants' alleged discovery, not how to find out how to use it, for themselves (see In re Gardner et al. 166 USPQ 138 (CCPA 1970). The specification only teaches what is intended to be done, but does not actually teach how to do that which is intended.

The examples in the specification do not disclose a therapeutic effect in the individuals after therapy with the said composition and/or the efficacy of the composition in treating cirrhosis of the liver. Furthermore, the specification does not provide specific guidance for producing a therapeutic effect using the claimed methods. Although working examples are not required, particularly in the predictable arts, the presence or absence of working examples is one factor that must be considered, particularly in the unpredictable arts. In the absence of specific guidance, one of skill in the art would be required to engage in undue experimentation to make and use the invention as claimed.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the breadth of the claims; (b) the nature of the invention; (c) the state of the prior art; (d) the relative skill of those in the art; (e) the level of predictability in the art; (f) the amount of direction provided by the inventor; (g) the existence of working examples; and (h) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue" (MPEP 2164.01 (a)).

In the instant case, claims 28-50 are drawn to a method of treatment by using the method for improving the efficiency of in vivo liver cell transduction, the said method comprising administering a composition comprising tri-iodothyronine (T3) and keratinocyte growth factor (KGF), and further comprising administering to the liver a retroviral vector complexed with the cationic liposome, DiOctadecylamidoGlycylSpermine or DOGS, subsequent to the induction of liver cell proliferation, thereby increasing transduction efficiency. The specification teaches only a method for improving the efficiency of in vivo liver cell transduction, but fails to disclose the efficacy of using the said method and composition in treating any disease and in particular, the specification does not disclose how to treat or prevent cirrhosis of the liver, which is the subject of claim 51.

Fujimoto (2000; Journal of Gastroenterology and Hepatology Vol. 15 (suppl.) D33-D36) in his review on "Gene Therapy for Liver Cirrhosis" states that the ideal

starategy for the treatment of liver cirrhosis should include prevention of fibrinogenesis, stimulation of hepatocyte mitosis, and reorganization of the liver architecture (see abstract, page D33). Ueki et al (1999; Nature Medicine, volume 5, no. 2, pp226-230) demonstrated that gene therapy with hepatocyte growth factor gene in rats was effective in inhibiting accumulation of fibrous connective tissue and pseudolobule formation and that HGF gene therapy prevented the apoptosis of hepatocytes and stimulated mitosis (page228, left column, last paragraph, lines 1-4), after administration of dimethylnitrosamine, which was used to induce cirrhosis in rats. Thus, it is clear that in addition to inducing liver cell proliferation, inhibition or prevention of pseudolobule formation and fibrinogenesis or resolution of fibrosis in a cirrhotic liver are needed to effectively treat or prevent cirrhosis of the liver. The method of instant invention results in liver cell proliferation, but the specification does not disclose its effectiveness in inhibiting or preventing fibrous tissue and pseudolobule formation, and/or its effectiveness in resolving the fibrosis that had already occurred in a cirrhotic liver, in order for the method to be effective in treating or preventing cirrhosis of the liver.

While the specification discloses formulations to make the pharmaceutical compositions, and methods of introduction of the pharmaceutical compositions, the specification does not teach what mode of administration would result in expression at the appropriate site, such that expression would be effective in treating or preventing a disease of the liver. There is no specific guidance regarding the amount of vector to be administered, the frequency of administration and level of expression required for the treatment to be therapeutically effective. While the method for improving transduction

efficiency does increase the levels of transduction, the specification does not disclose how the increased transduction levels would lead to the treatment and/or prevention of a disease of the liver in a subject. The specification does not teach how to use the invention as claimed. Even though the skill of an artisan in this subject area is considered to be very high, it would require undue experimentation on the part of an artisan to make and use the invention as specified and use the invention as claimed. The specification and the working examples do not provide sufficient guidance to practice the invention as claimed.

Therefore, in the absence of specific guidance and working examples, the use of the claimed composition and the method in the treatment and prevention of a disease of the liver is unpredictable. In such a situation, one skilled in the art would not know how to use the invention as claimed, without undue experimentation. In view of the limited guidance in the specification, and limited working examples, and the unpredictability of the art, one skilled in the art would be required to engage in undue experimentation, in order to use the invention over any scope as claimed.

At the time of filing, gene therapy utilizing the direct administration of recombinant nucleic acids, whether in the form of retroviruses, adenoviruses, or plasmid DNA/liposome complexes, was considered to be highly unpredictable. Verma et al. states that, "[t]he Achilles heel of gene therapy is gene delivery..", and that, "most of the approaches suffer from poor efficiency of delivery and transient expression of the gene" (Verma et al. (1997) Nature, Vol. 389, page 239, column 3, paragraph 2). Marshall concurs, stating that, " difficulties in getting genes transferred efficiently to target cells-

and getting them expressed- remain a nagging problem for the entire field", and that, "many problems must be solved before gene therapy will be useful for more than the rare application" (Marshall (1995) Science, Vol. 269, page 1054, column 3, paragraph 2, and page 1055, column 1). Orkin et al. further states in a report to the NIH that, " .. none of the available vector systems is entirely satisfactory, and many of the perceived advantages of vector systems have not been experimentally validated", and that," [w]hile the expectations and the promise of gene therapy are great, clinical efficacy has not been definitively demonstrated at this time in any gene therapy protocol" (Orkin et al. (1995) "Report and recommendations of the panel to assess the NIH investment in research on gene therapy", page 1, paragraph 3, and page 8, paragraph 2). Among the many factors that the art teaches affect efficient gene delivery and sustained gene expression are anti-viral immune responses, particularly against adenoviral proteins, and the identity of the promoter used to drive gene expression. Verma et al. teaches that weak promoters produce only low levels of protein, and that only by using appropriate enhancer-promoter combinations can sustained levels of therapeutically effective protein expression be achieved (Verma et al., *supra*, page 240, column 2). Verma et al. further warns that, " .. the search for such combinations is a case of trial and error for a given type of cell" (Verma et al., *supra*, page 240, bridging sentence of columns 2-3). Thus, the art at the time of filing clearly establishes that expectation for achieving a desired therapeutic effect *in vivo* by expressing a therapeutic gene using any of the expression constructs known in the art at the time of filing was extremely low.

Further, Davern et al. (1998; Digestive diseases, vol.16, pp23-37), in their review on "Gene Therapy for Liver Disease", highlight the obstacles that must be addressed before hepatic gene therapy becomes a reality (see abstract). Davern et al. (1998) state that an important concern with using retroviral vectors in gene therapy is their destructive interactions with the host immune system through foreign antigens including both viral proteins and murine glycoproteins on the surface of the viral envelope (page 30, left column, bottom paragraph, lines 1-5). Davern et al. (1998) state that a major barrier to direct in vivo injection of retroviral vectors has been the brisk complement-mediated destruction of the virions by antibodies directed at non-human galactose components of murine glycoproteins within minutes of exposure to human serum (page 30, bridging paragraph of left and right columns). They further state that efforts of gene therapy for correcting genetic defects in the liver and other organs have fallen short of the initially lofty expectations and that the gene therapy is a Herculean task when one considers that evolution has equipped all cells, normal or otherwise, to desperately resist such manipulation (page 35, concluding paragraph).

Thus, due to the art recognized unpredictability of achieving therapeutic levels of gene expression following direct or indirect administration of nucleic acid vectors, and the unpredictability of extending the results of animal systems to humans, the lack of guidance provided by the specification for the parameters affecting delivery and expression of therapeutic amounts of DNA into the cells, the lack of guidance concerning the treatment of cirrhosis of the liver using the composition of the instant invention, it would have required undue experimentation to practice the instant invention

and the skilled artisan would not have predicted success in treating or preventing diseases of the liver as claimed. Thus the specification does not enable one skilled in the art to use the claimed invention in a method for treating.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 26-51 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 26-34 are indefinite in their recitation of "concurrently" because only a single composition is administered or contacted with the liver cells and thus it is unclear what else is concurrently administered or contacted. Deleting the term "concurrently" is suggested.

Claims 28-50 are indefinite in their recitation of "the RNA, protein or polypeptide to be expressed" because there is no antecedent basis for this phrase.

Claims 29 and 30 are indefinite in their recitation of "further comprising inducing the liver cell proliferation in vitro" (or "in vivo") because it is unclear if this is an additional step such that there are now two steps where liver cell proliferation is induced or if there is only one step where liver cell proliferation is induced. If only one step, use of claim language reciting "wherein the liver cell proliferation is induced in vitro" (or "in vivo") is suggested.

Claim 31 is indefinite in its recitation of "wherein the RNA comprises ribozymes" because it is unclear if the claim is intended to be limited to the use of a retroviral vector encoding a ribozyme. As written, the claim still allows for the vector to encode protein or polypeptide.

Claim 32 is indefinite in its recitation of "wherein the RNA comprises anti-sense RNA" because it is unclear if the claim is intended to be limited to the use of a retroviral vector encoding an anti-sense RNA. As written, the claim still allows for the vector to encode protein or polypeptide.

Claims 35-50 are indefinite in their recitation of "the condition" because there is no antecedent basis for this phrase.

Claim 35 is indefinite in its recitation of the phrase "a the nucleic acid". The meaning of the phrase is not clear.

Claim 40 is indefinite in its recitation of the phrase "by weight". It is not clear whether the phrase is referring to the subject or to T3 and/or to KGF by weight.

Claims 47 and 48 are indefinite in their recitation of "the retroviral vector further comprising a cationic liposome". The vector cannot comprise a liposome. It is suggested that amending the wording of the claim 47 to "the retroviral vector complexed with a cationic liposome" would make the meaning of the claim clear.

Claims 49 and 50 are indefinite in their recitation of "pharmaceutical composition" because there is no antecedent basis for this phrase. Claim 35, from which they depend, recites only a "composition".

Claim 51 is indefinite in its recitation of "concurrently administering to a subject a composition comprising...." Because only a single composition is administered and thus it is unclear what else is being administered concurrently.

Claim 51 is indefinite in that it is incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: the conclusory statement at the end of claim 51 does not correspond to the preamble. The preamble recites "a method for treating or preventing cirrhosis of the liver" but the conclusion recites "thereby inducing a semi-synchronous wave of liver cell proliferation in vivo." Thus, the conclusion does not correspond to the preamble and the claim is rendered confusing and indefinite.

Conclusion

Claims 26-51 are not allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sita S Pappu whose telephone number is (703) 305-5039. The examiner can normally be reached on Mon-Fri (9:00 AM - 5:00 PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Clark can be reached on (703) 305-4051. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 746 7442 for regular communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist at (703) 305-2758.

S.Pappu
January 11, 2002

Anne-Marie Baker
ANNE-MARIE BAKER
PATENT EXAMINER